RISKS IN MASS DISTRIBUTION OF POTASSIUM IODIDE*

ROSALYN S. YALOW, PH.D.

Solomon A. Berson Research Laboratory
Veterans Administration Medical Center
Bronx, New York

THE determination whether and under what circumstances mass potassium iodide (KI) prophylaxis is desirable in the event of a nuclear power plant accident depends in large part on perception of the relative toxicities of thyroidal radioiodines at anticipated uptake levels and the potential hazards of mass distribution of KI to a medically unsupervised population. None of us would question that, in some cases, blockage with KI or its equivalent is desirable to prevent thyroidal accumulation of radioiodines. But the issue presently under consideration is not administration of KI to a controlled, medically supervised group of workers who may be occupationally exposed *frequently* or *continuously* to radioiodines, people such as those of us who regularly prepare radioiodine labeled materials such as peptides. The question rather is the advisability of general distribution to a population which may be alarmed by fear of radiation at any level and is poorly informed concerning the potential hazards of taking or not taking the drug.

Data concerning the toxicity of radioiodines to humans are derived largely from studies of the sequelae of previous exposure of several groups: those directly exposed at Hiroshima and Nagasaki; the Marshallese Islanders who, unfortunately, were the victims of fall-out from a hydrogen bomb test; people in Utah and Nevada exposed to fall-out from the Nevada tests during the 1950s; and those receiving tracer or therapeutic doses of ^{131}I for medical reasons.

The largest human experience with radioiodine is that of the millions who received tens of microcuries of ^{131}I for the diagnosis of thyroid disease as well as the few hundred thousands treated for hyperthyroidism with millicuries of [131]I. It has been estimated[1] that during the 20 years

following the ready availability of ^{131}I from the Oak Ridge Reactor, more than 200,000 people received therapeutic doses of this isotype. If experience at my hospital is typical, the number of diagnostic tracer doses probably exceeded the number of therapeutic doses by at least a factor of 10. The dose to the thyroid during the early diagnostic studies averaged about 100 rem.

There has been no systematic follow-up for radiation-induced malignancy in all or even most of these several million patients. However, thyroid cancer remains a rare disease. The death rate from this malignancy is only about 1,000/year, and the rate has not changed over the past two decades. Thus, it is most unlikely that cancer of the thyroid is associated with exposure of the adult thyroid gland to 100 rem of ^{131}I irradiation. Recently a follow-up has been reported of a small subset of these patients. Holm et al.[2] have reported a retrospective study of over 10,000 patients in Sweden who received an average of 60 μCi ^{131}I and a thyroidal dose of about 60 rem between 1952 and 1965 for diagnostic purposes. Tracer studies were performed mainly on adults; only 5% of the patients were under 20 years at the time of ^{131}I administration. Between 1958 and 1977 nine patients were diagnosed to have a thyroid malignancy five or more years after administration of [131]I. The expected incidence in a population of 10,000, according to figures from the Swedish Cancer Registry, was 8.3. The mean follow-up period for the patients averaged 18 years, ranging from 10 to 25 years. The risk factors used by the United Nations Scientific Committee on the Effects of Atomic Radiation,[3] which were derived from studies at high dose rates and from external x-radiation, predict an excess of 50 to 150×10^{-6} thyroid malignancies per person-rem within 25 years of radiation, with an equal number to be detected subsequently. Were this valid, then in this group one would have expected an excess of 30 to 90 thyroid malignancies by 25 years, yet no excess was observed by 18 years. The risk factor based on the Hiroshima-Nagasaki experience, 14×10^{-6} malignancies per person-rem, is lower than that based on external radiation, but still is quite high compared to the ^{131}I experience. Thus, there is every reason to believe either that the danger of x-ray exposure to the thyroid has been overestimated or that delivering radiation at a lower dose rate is less effective in producing malignancies for the same total dose. For instance, Ullrich and Storer[4] have shown that there is no measurable increase in the incidence of ovarian tumors in REM mice receiving a 50 rem dose at the rate of 8.3 rem/day compared to unirradiated controls. However, there was an increase of 30% in ovarian tumor

incidence if the same cumulative dose were delivered at the rate of 45 rem/minute. It is evident from many studies such as this that dose rate as well as cumulative dose should be factored into any estimate of possible radiation-induced malignancies.

It had been estimated that the fallout from the Nevada testing was responsible for an average cumulative thyroid dose to all children in Utah of 46 rem; children in southwestern Utah were estimated to have received more than 100 rem.[5] However, a study[6] of more than 5,000 control and exposed children examined by a group of distinguished thyroidologists concluded that there was no significant difference in any type of thyroid disease between exposed children in Utah and Nevada and unexposed children in Utah and Arizona. The examinations were begun in 1965, 12 years after the heaviest known exposure to fallout, and continued annually for six years. Thus, the follow-up period was sufficiently long for induction of thyroid cancers if there were to be any due to the fallout from the testing. Only two cases of thyroid carcinomas were detected among the examined adolescents, and these occurred in subjects who were not living in the primary fallout area during infancy. Using United Nations risk factors, seven to 21 thyroid malignancies would have been expected in the group of almost 1,400 who were very young children when exposed. Yet, in 18 years not one was observed. In fact, there was no increase even in thyroid nodules among the exposed group. Thus, these observations in children exposed to ^{131}I are consistent with the observations in adults receiving ^{131}I tracer tests and suggest that the risk factors estimated from x-radiation are much too high. It would appear also that there are no evident differences in sensitivity between children and adults receiving ^{131}I exposure.

The studies just described are the only ones reporting on a large series of humans receiving thyroidal ^{131}I exposures in the 50-100 rem range. The Marshall Islanders were unfortunate victims of a tragic accident and were unexpectedly exposed in 1954 to heavy fall-out from bomb testing. Many of them developed thyroid disease. The exposed group was estimated to have received about 175 rem whole body gamma radiation and thousands of rem to the skin. Significant amounts of radionuclides were absorbed by inhalation and consumption of contaminated food and water. Calculation of the thyroid doses were based on a single pooled urine sample collected from the Rongelap people 15 days after exposure when the shorter lived radioiodines had decayed.[7] The dose to the thyroids of the children was estimated to range from 700 to 1,400 rem. This estimate may well be too

low in view of the subsequently documented high incidence of hypothyroidism.[7] Among the children less than 10 years at time of exposure, the incidence of benign adenomas was quite high (18 in 23), and one child had a thyroid malignancy. It is of interest to speculate that if the hypothyroidism had been recognized and prophylaxis initiated earlier, the apparently high incidence of nodularity and carcinogenesis may well have been preventable since it has been suggested that prolonged endogenous TSH stimulation associated with hypothyroidism may serve as an inducer and promoter in the development of metastatic thyroid carcinoma.[8]

Let us now consider the prevalence and significance of occult thyroid cancer, i.e., tumors, less than 1.5 cm in diameter.[9] This cannot be measured directly in an intact living population but can be inferred from the rates obtained from surgical or autopsy specimens. The data suggest that thyroid cancer death rates appear to be lowest in regions where occult thyroid cancer is highest. Thus, in Switzerland, the United States, and Japan the thyroid cancer death rates are 1.5, 0.6 and 0.3 per 100,000 per year respectively; the incidence of occult thyroid cancer at autopsy employing similar methods was 1.2%, 5.7% and 17.9%.[9] The observations that the highest rates of fatal thyroid cancers are found in countries which historically are iodine deficient suggests that differences in TSH levels may be important in determining whether a thyroid nodule develops to a malignant state. Whether or not occult thyroid cancers are found appears to be related to how carefully they are looked for. The Japanese experience is that the observed prevalence is almost 30% when the total thyroid is serially blocked and less than 5% when only routine slides are made.[9]

In view of the high incidence of occult thyroid cancer, the question may be raised as to whether the reported[10] increasing incidence of thyroid cancer, which has been attributed to childhood x-radiation, is real or artifactual. The National Cancer Institute has recommended that programs be initiated to locate, recall, and examine a population presumed to be at risk for development of thyroid cancer, e.g., those who had received external head, neck, and chest radiation. Royce et al.[11] responded to this recommendation by attempting to recall 738 patients so radiated, and about one third of those recalled replied. This study was unusual in that those who came for examination were asked to bring a sibling of the same sex who was close in age or a nonsibling of the same sex and approximate age as a control for comparison studies. What was also unique about this study was that neither of the two examining endocrinologists was aware of the irradiation history of the examinee nor the other examiner's findings.

The irradiated patients had received radiation doses averaging 450 to 750 rem. There were 25 clinically abnormal thyroids among 214 irradiated subjects and 20 among the 243 controls. Only four controls and six irradiated subjects agreed to surgical operation. Histological diagnosis of these 10 revealed two papillary carcinomas among the control subjects and none among the irradiated subjects. The sample size was small and most of the subjects were over 21. Further, only one third of the patients solicited replied and were examined.

Nonetheless, it is quite clear from this study that so-called prevalence of palpable thyroid abnormalities in previously irradiated subjects appears to depend on the examiner's knowing the history, thus introducing examiner bias. Thyroidologists appreciate that the distinction between normal thyroid and enlarged thyroid and between nodular and diffuse enlargement is often difficult and not uniformly agreed upon among different observers. It is, therefore, not unexpected that an observer, knowing of a history of irradiation and faced with the recallee's concern, might tend to overdiagnose in the interests of what might be considered to be conservative management. It is therefore not impossible that at least some of the apparent increasing incidence of thyroid cancer simply represents discovery, because of overzealous and unnecessary intervention, of the thyroid cancers already present in 6% of the population of the United States.[9] Perhaps the general acceptance of enhanced tumorogenic potential of x rays compared to ^{131}I may be a consequence of the program of recall and intervention rather than of actual x-radiation-induction of thyroid cancers.

Let us now consider the reverse side of the problem, i.e., is KI really benign? In National Council on Radiation Protection Handbook 55[12] an estimate was made that about 48 million 300 mg doses of KI are produced per year in the United States. Based on the Food and Drug Administration data of 24 reactions reported to them each year, the reaction risk was calculated as 24 reactions/48 million doses. However, KI therapy is not given to 48 million persons each year. The major fraction of patients receiving KI receive several doses each day throughout the year so that the reaction rate *per patient* is at least a thousandfold higher. If 48,000 new patients were to start on KI each year and if there were 24 reactions, there would be an incidence of 5 reactions per 10,000 persons, this could hardly be considered negligible if KI were to be administered to millions of people. In fact, since most reactions to a drug such as KI are not reported to the F.D.A. and we do not know how many patients are started each

year on KI, there is no way at present to estimate the risk. The report[12] goes on to state that "an additional indication of the lack of toxicity of stable iodine in relation to radioiodine is illustrated by the recommendation that it is used to prevent radioiodine uptake when the ^{125}I-labeled fibrinogen test is employed." However, Denham and Himsworth[13] had earlier reported that three of 31 geriatric patients developed biochemical hyperthyroidism after receiving 120 mg KI/day for two to three weeks. In each case the condition was superimposed upon a background of ischemic heart disease. These investigators therefore suggested that the induction of hyperthyroidism by iodides might not be rare in the elderly. Further, Curd et al.[14] reported a very high incidence of iodide sensitivity during a study of the turnover of radioiodide labeled serum proteins in a special group of patients, these with rheumatoid arthritis, lupus, and others with autoimmune related diseases. Four of 57 such patients had severe reactions and in one the outcome might have proved fatal had it occurred in other than a hospital setting. They concluded that KI can precipitate life-threatening systemic illness in sensitive persons. Characteristic of their patients was hypocomplementic vasculitis, but one cannot conclude that only such patients have acute sensitivity reactions to KI.

More than a quarter century ago Peacock and Davison[15] reviewed earlier reports of iodide sensitivity, distinguishing between those due to chronic overdosage and those with true hypersensitivity. Included in the historical summary were occasional cases of periarteritis nodosa, thrombocytopenic purpura, and multiple cases of severe iododerma. They then examined 502 charts of asthmatic patients seen in their own practice over a two-year period. The incidence of reactions was 16%, almost all of whom had reactions sufficiently severe to warrant discontinuance of the drug; severe dermatitis was the most common finding. In a report[16] on drug-induced dermatologic reactions in more than 15,000 patients monitored by the Gainesville Drug Study Group, it was noted that KI was second only to the penicillins in inducing such reactions; the incidence ranged from 1.2 to 2.3% for the penicillins and was about 1% for KI.

This short review cannot record the multiplicity of papers describing acute reactions following a short period of even small doses of iodides. Problems associated with chronic overdosage probably are not relevant, therefore, conditions such as iodide goiter of the newborn or iodide-induced hypothyroidism are not considered. Adverse reactions reported to the F.D.A. are not representative of the toxicity of this drug. It would certainly have been advisable to have established a central registry of side

effects from KI before recommending its distribution to large numbers of people. For instance, the incidence of hypocomplementic vasculitis and rheumatoid arthritis is estimated to be about 6 in 10,000 people. If the report of Curd et al.[14] is valid, and such people had received KI at the time of the Three Mile Island Accident, some would have had an acute, severe, medically unsupervised reaction during a time of mass hysteria. Without proper medical intervention, there might even have been a fatality. Yet no one among the general public had any measurable uptake of radioiodine. If this proposal had been followed, KI would have been administered to those on Three Mile Island and distributed to everyone living within a 10-mile radius of the reactor. This might have resulted in a real medical disaster, not simply psychological problems associated with needless fear. It might have resembled the swine flu fiasco—where a danger did not exist—but the purported prophylaxis cost not only a fortune in money and manpower, but also in lives.

It is evident from this brief review that the potential danger of low dose ($\sim$ 100 rem from radioiodines) thyroidal radiation has been exaggerated. It is equally evident that the potential dangers of administration of KI has not been fully considered. Some critical questions are: what is the probability of sufficient release of radioiodines to make them represent the sole or major radiation hazard in the event of a nuclear accident; which group would potentially be affected by the radioiodines; how can those likely to suffer severe immediate morbidity or mortality from KI administration be identified; what distribution method could be used to assure that only those likely to receive excessive thyroidal exposure, but not likely to have hypersensitivity reactions to KI, have access to the drug.

The public has been frightened by lurid tales about a plume of radioactivity descending to earth hundreds of miles from a reactor if an accident were to occur. They have not been informed about the potential problems associated with KI and have been misinformed about its value because any release of radioiodines would be accompanied by other radioisotopes of equal or greater concern. A more sensible plan for protection from all of these in the extremely unlikely event of a catastrophic reactor accident would be to remain indoors, preferably in a building with minimum air exchange with the outside, and await directions from authorities who should be informed by appropriate radiation monitoring concerning potentially hazardous levels of radiation.

REFERENCES

1. Saenger, E. L., Thoma, G. E., and Tompkins, E. A.: Incidence of leukemia following treatment of hyperthyroidism. *J.A.M.A. 205:* 147-54, 1968.
2. Holm, L.-E., Lundell, G., and Wallnder, G.: Incidence of malignant thyroid tumors in humans after exposure to diagnostic doses of iodine-131. 1. Retrospective cohort study. *J. Nat. Cancer Inst. 64:* 1055-59, 1980.
3. United Nations Scientific Committee on the Effects of Atomic Radiation: *Sources and Effects of Ionizing Radiation.* New York, 1977, pp. 361-423.
4. Ullrich, R. L. and Storer, J. B.: Influence of Dose, Dose Rate and Radiation Quality on Radiation Carcinogenesis and Life Shortening in RFM and BALB/c Mice. In: *Late Biological Effects of Ionizing Radiation.* Vienna, International Atomic Energy Agency, 1978, vol. 2, pp. 95-113.
5. Tamplin, A. R. and Fisher, H. L.: Estimation of Dosage to Thyroids of Children in the U.S. from Nuclear Tests Conducted in Nevada During 1952 Through 1965. UCRL, 14707. Livermore, CA, Lawrence Radiation Laboratory, 1966.
6. Rallison, M. L., Dobyns, B. M., Keating, F. R., et al.: Thyroid disease in children. Survey of subjects potentially exposed to fallout radiation. *Am. J. Med. 56:* 457-63, 1974.
7. Conrad, R. A.: Summary of Thyroid Findings in Marshallese 22 Years After Exposure to Radioactive Fallout. *In: Radiation Associated Thyroid Carcinoma,* DeGroot, L. J., editor. New York, Grune and Stratton, 1977, pp. 241-57.
8. Beierwaltes, W. H.: The Natural History of Thyroid Cancer. *In: Radiation Associated Thyroid Carcinoma,* DeGroot, L. J., editor. New York, Grune and Stratton, 1977, pp. 63-74.
9. Sampson, R. J.: Prevalence and Significance of Occult Thyroid Cancer. *In: Radiation Associated Thyroid Carcinoma,* DeGroot, L. J., editor. New York, Grune and Stratton, 1977, pp. 137-53.
10. Pottern, L. M., Stone, B. J., Day, N. E., et al.: Thyroid cancer in Connecticut, 1935-1975: An analysis by cell type. *Am. J. Epidemiol. 112:* 764-74, 1980.
11. Royce, P. C., MacKay, B. R., and DiSabella, P. M.: Value of postirradiation screening for thyroid nodules. *J.A.M.A. 242:* 2675-78, 1979.
12. National Council on Radiation Protection and Measurements: *Protection of the Thyroid Gland in the Event of Releases of Radioiodine.* NCRP Report No. 55. Washington, D. C., 1977.
13. Denham, M. J. and Himsworth, R. L.: Hyperthyroidism induced by potassium iodide given in the course of ^{125}I-fibrinogen test. *Age Ageing 3:* 221-25, 1974.
14. Curd, J. G., Milgrom, H., Stevenson, D.D., et al.: Potassium iodide sensitivity in four patients with hypocomplementic vasculitis. *Ann. Intern. Med. 91:* 853-57, 1979.
15. Peacock, L. B. and Davison, H. M.: Observations on iodide sensitivity. *Ann. Allergy 15:* 158-164, 1957.
16. Steward, R. B., May, F. E., and Cullen, S. I.: Dermatologic adverse drug reactions in hospitalized patients. *Am. J. Hosp. Pharm. 36:* 609-12, 1979.